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Translational relevance of rodent models of hypothalamic-pituitary-adrenal function and stressors in adolescence

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ABSTRACT

Elevations in glucocorticoids that result from environmental stressors can have programming effects on brain structure and function when the exposure occurs during sensitive periods that involve heightened neural development. In recent years, adolescence has gained increasing attention as another sensitive period of development, a period in which pubertal transitions may increase the vulnerability to stressors. There are similarities in physical and behavioural development between humans and rats, and rats have been used effectively as an animal model of adolescence and the unique plasticity of this period of ontogeny. This review focuses on benefits and challenges of rats as a model for translational research on hypothalamic-pituitary-adrenal (HPA) function and stressors in adolescence, highlighting important parallels and contrasts between adolescent rats and humans, and we review the main stress procedures that are used in investigating HPA stress responses and their consequences in adolescence in rats. We conclude that a greater focus on timing of puberty as a factor in research in adolescent rats may increase the translational relevance of the findings.

Contents

1. Introduction

Glucocorticoid hormones (mostly cortisol in humans and corticosterone in rats), the release of which is under the control of

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the hypothalamic-pituitary-adrenal (HPA) axis, initiate mechanisms that enable the individual to adapt to the immediate demands of the environment. For example, elevations in glucocorticoids that result from the activation of the HPA axis in response to stressors have immunosuppressive and anti-inflammatory effects, influence lipid and glucose metabolism, and inhibit reproductive functions. In the CNS, through actions on neurogenesis, synaptic and dendritic remodeling, neurotransmission, and learning and memory functions, glucocorticoids shape future brain function and behaviour. Programming effects of stress exposures on the developing fetus provide a means by which glucocorticoids experienced in early life have effects across the lifespan and possibly into future generations (Bale, 2014; Meaney et al., 2007). The preclinical literature has made great inroads into mechanisms involved in the maladaptive consequences of excessive glucocorticoid exposures in early life and in adulthood that result from repeated or chronic stressors, or a severe stress exposure. So, why the interest in the adolescent period, an interest that has grown exponentially in the last 15 years?

Adolescence is of great clinical importance. It is the time in which many mental health problems such as mood disorders emerge. Further, the risk of drug abuse and addiction is greater from drug exposures in adolescence than in adulthood (e.g., Blomeyer et al., 2013). The clinical problems of many adult psychiatric patients originate in adolescent experiences (Oldehinkel and Bouma, 2011). In adolescents, as in adults, atypical HPA function and/or a history of stress exposures, are precursors to clinical depression (Guerry and Hastings, 2011). Thus, the growing interest in the adolescent period is tied to understanding risks that might be associated specifically with this time of life, a time that had been relatively neglected by researchers (Grant et al., 2003) until recently. Further, the idea that developmental plasticity (defined as a lasting phenotypic change in response to cues received in the past, Fawcett and Frankenhuis, 2015) was greatest during critical periods of prenatal and neonatal life and diminished thereafter with age is confronted with evidence that there are a series of sensitive periods across the lifespan in many species. Adolescence, specifically, has been cast as a sensitive period for the development of social functions in species as diverse as zebra finches (Ruploh et al., 2014), guinea pigs (Sachser, 1992), rats (McCormick et al., 2015), and humans (Blakemore, 2012), among others. Challenges to the view that adolescence was a specialization unique to humans (e.g., Bogin and Smith, 1996) also promoted the possibility of animal models for understanding human adolescence.

The importance of animal models for understanding mental health is well documented (Stevens and Vaccarino, 2015). This review focuses on benefits and challenges of rats as a model for translational research on hypothalamic-pituitary-adrenal function and stressors in adolescence, highlighting important parallels and contrasts between adolescent rats and humans. We also review the main stress procedures that are used in investigating HPA function and stress in adolescence in rats, and factors that should be considered for rat models of adolescent stress for translational research.

2. Pubertal development in humans and rats and the definition of adolescence

Adolescence involves a transition between childhood and adulthood, and requires a reorganization of a physiology and a behaviour repertoire that is adapted to one ontogenetic period to enable adaptations for a new ontogenetic period during which reproductive function is attained. As such, one of the important hallmarks of the adolescent period is puberty. Although there is some independence between adolescent development and the onset of puberty in that some maturational processes in the brain occur irrespective of a pubertal rise in gonadal function (Sisk and Foster, 2004), the importance of puberty to adolescence cannot be overstated. The World Health Organization defined adolescence in humans as people between the ages of 10 and 19 years, with the onset of puberty marking the transition from childhood to adolescence (http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/).

Puberty begins at about 8–10 years of age in girls and about a year later in boys and involves a rise in kisspeptin signaling, which results in increased gonadotrophin releasing hormone release, the hypothalamic hormone of the hypothalamic-pituitary-gonadal pathway (Cortés et al., 2015). The increase in estrogenic function results in the development of breast buds in girls typically between the ages of 10 and 11 years, and menarche at about 12 years of age (Parent et al., 2003). Menarche is a relatively late manifestation of puberty that usually (but not always) is preceded by the first ovulation (Cortés et al., 2015). Further, the mean age of onset of menarche is later in underprivileged populations than in “well-off” populations (Parent et al., 2003). An increase in testicular volume is an early marker of pubertal onset in boys, and the mean age of the time of this increase is 11.5 years (Lee et al., 2010). The completion of spermatogenesis is the culmination of puberty in boys. Another feature of the pubertal process in both girls and boys is a peak in growth velocity. Growth in height ceases in girls 4–5 years after menarche at a median age of 17.3 years (Spear, 2002). The growth velocity is higher in boys and growth in height stops at a median age of 21.2 years (Spear, 2002). A 4–5 year age range in pubertal onset is considered normal variation in both sexes (Parent et al., 2003). The variation in onset of puberty in humans relative to mean life expectancy, however, is negligible compared with that in other mammals, and rats in particular (Bronson and Rissman, 1986).

One of the challenges of a preclinical model of adolescence is defining the ages that are comparable to humans. Adolescence in rats has been defined liberally as being from postnatal day (PND) 21–59 (Tirelli et al., 2003) and conservatively as being from PND 28 to 42 (Spear, 2000). There are similarities and differences in the pubertal process of rats and humans. For example, whereas the gonads are quiescent until puberty and spermatogenesis only begins at puberty in humans (Plant, 2015), in Wistar rats, spermatogenesis was found to begin at postnatal day 5 and completed at PND 43 (van Haaster and de Rooij, 1993). Comparable to the growth spurt in adolescent humans, rats have a steep increase in the length of the tibia in both males and females from about PND 25–60 and a less steep rise thereafter until reaching asymptote at about PND 175 (Horton et al., 2008). Growth rates (μm/day) in the length of the tibia are highest at about PND 45. Nevertheless, rats do not have the quiescent period in growth that is evident in humans prior to the pubertal growth spurt. Instead, in rats, skeletal growth is continuous and displays an exponential trajectory that decays at about PND 64 (Horton et al., 2008). Other markers of pubertal development than growth trajectories, however, are more commonly used in studies of adolescent rats.

Physical markers of puberty in rats that coincide with increased hypothalamic-pituitary-gonadal function are the onset of vaginal opening in females, which coincides with a surge in estradiol and the onset of ovulation (Castellano et al., 2011; Ojeda and Urbanski, 1994), and balanopreputial separation in males, which coincides with a rise in androgen concentrations and with sperm in the epididymis (reviewed in McCormick and Mathews, 2010). Regular estrous cycles typically are evident about a week after vaginal opening, and sperm production is optimal only several weeks after balanopreputial separation (Lohmiller and Sonya, 2006). Although the ages of PND 25–42 in rats has been suggested to be analogous

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to the ages of 10–18 years in humans (Saalfield and Spear, 2016; Spear, 2015), this time span would involve mostly a prepubertal period in females based on age at vaginal opening and in males based on age at balanopreputial separation, which is inconsistent with the post-pubertal definition of adolescence for humans. Nevertheless, the overwhelming majority of research into the adolescent period has been conducted in prepubertal male rats.

Korenbrot et al. (1977) reported that about 50% of Sprague Dawley male rats had attained balanopreputial separation by PND 40 or PND 43 (in two graphs of different samples), and that 50% had mature motile sperm by about 47 days of age. They found an increase of about 20% in circulating androgen (testosterone and dihydrotestosterone) from PND 30 to 40, after which there was a steep increase (more than 200%) from PND 40 to PND 60 (Korenbrot et al., 1977). A more recent study with Sprague Dawley rats has results consistent with those of Korenbrot et al. (1977): No Sprague Dawley female had a vaginal opening at PND 28, just over 20% had vaginal openings at PND 32 and 100% had vaginal openings at postnatal day 36 (Vetter-O'Hagen and Spear, 2012). For Sprague Dawley males, none had balanopreputial separation at PND 36, about 60% did at PND 40, and 100% did at PND 48 (Vetter-O'Hagen and Spear, 2012). There was a gradual increase in estradiol from PND 28 to PND 48, at which point there was no further increase, and the increase from PND 28 was significant only by PND 40. Detectable concentrations of testosterone were only obtained at PND 40 (approx. 0.25 ng), and rose to about 1.3 ng/mL at PND 48, and rose again to about 2.5 ng/mL in PND 75 rats (Vetter-O'Hagen and Spear, 2012). Others have reported estradiol to peak at PND 35 in females, but this may be in part because of the use of a different strain of rats (Wistar rats) (Zapatero-Caballero et al., 2004). Across different strains of males, however, the pattern of a slight rise to about PND 45, and a rise again to adult concentrations at about PND 60 is the typical result (Wistar rats, Pignatelli et al., 2006; Zapatero-Caballero et al., 2003).

There are strain differences in the age at which specific male sexual behaviours (e.g., genital grooming, intromission) are demonstrated, which are thought to reflect, in part, strain differences in pubertal development (Hernandez-Gonzalez, 2000). Long Evans rats are reported to attain reproductive milestones earlier than do Wistar rats (Hernandez-Gonzalez, 2000). A recent study reports the mean age of vaginal opening in Long Evans rats to be PND 34.9, with a range of 32–38, and the mean age of balanopreputial separation to be 44.9, with a range of 42–48 (Drzewiecki et al., 2016). We find a similar mean age for vaginal opening in Long Evans female rats from a different supplier (Charles River rather than Harlan), 34.4 days, although we found a wider range in days (30–40, unpublished observations). In addition, we found no effect of daily injection stress or of daily 1 h isolation/restraint stress beginning at PND 30 on mean day of vaginal opening (unpublished observations), although there is evidence in the literature of effects of chronic stressors on timing of puberty in both humans and rodents (Parent et al., 2015). We have not investigated age of balanopreputial separation systematically, although when we have examined our Long Evans males at PND 46, all had reached this milestone. A direct comparison of two strains of males and females found an earlier onset of puberty in Long Evans than in Wistar rats in both sexes (Keeley et al., 2015).

A potential caveat in using physical markers as indicators of pubertal status is that environmental factors can disrupt the linkage between the outward physical markers and inner physiology. For example, first estrous varied from a mean age of PND 36.5 to 44.9 depending on housing conditions (grouped or not, presence of male or not) without a similar effect on day of vaginal opening (mean of 35.6–36.1 across groups) (Vandenbergh, 1976). Thus reliance on external physical markers to determine pubertal status may be problematical in some experimental designs.

These studies of pubertal development in rats highlight a number of considerations for their use as translational models. First, when using rats as a model for human adolescence, there should be greater focus on the time post-puberty. This point does not detract from the importance of the prepubertal period; there is much evidence that prepubertal rats differ from adult rats in the experience of and consequences of exposure to stressors (see reviews by Green and McCormick, 2013b; McCormick and Green, 2013). Nevertheless, there also is evidence that postpubertal rats differ from both prepubertal and adult rats: for example, in response to amphetamine (Mathews et al., 2011); in expression of tyrosine hydroxylase in the caudate nucleus and medial prefrontal cortex (Mathews et al., 2009); in HPA function and its regulation by testosterone release (Green et al., 2015, 2016); in testosterone's influence on sonic hedgehog signaling (Bond et al., 2010); in corticotropin releasing factor receptor expression in various brain regions (Lukkes et al., 2016); in performance on associative learning tasks and D1 receptors in the orbitofrontal cortex and in piriform cortex (Garske et al., 2013).

Another important example is in the investigation of differences between prepubertal and postpubertal rats in sensitivity to reward; an argument that has been made in favour of rats as an animal model for investigating adolescence is that both adolescent rats and adolescent humans differ from their adult counterparts in motivation and reward (higher reward sensitivity to both natural and drug rewards in the younger age groups than in the adult age groups) (Doremus-Fitzwater et al., 2010). Many such adolescent versus adult comparisons, however, have involved prepubertal and adult rats (e.g., Doremus-Fitzwater et al., 2012; Hammerslag and Gulley, 2014; Torres et al., 2008). In a study of reward value of palatable foods, the intake of sweetened condensed milk by male rats during a 15 min period of intermittent access increased to a peak at PND 50 after which there was a steep decline to PND 70 (Friemel et al., 2010). Postpubertal PND 50 rats displayed more lever presses in a progressive ratio test of motivational incentive than did pre-pubertal PND 40 and adult PND 70 rats, which did not differ (Friemel et al., 2010). Reward sensitivity thus was greatest during the restricted period of puberty than either before or after in rats, which suggests that the postpubertal rat may provide the best comparison for human adolescents. During adolescence, humans also show higher preferences for sweet tastes (Desor and Beauchamp, 1987) and have a higher intake of calories relative to body weight than in adulthood (Post and Kemper, 1993), which parallels the results found in rats.

In sum, the majority of research in adolescence in rats has involved primarily male rats in the prepubertal phase of adolescence. Nevertheless, postpubertal rats may provide the best model for translational research.

3. Hypothalamic-pituitary-adrenal (HPA) function in adolescence in humans and rats

In humans, there is a rise in baseline HPA function and reactivity after puberty in both sexes (Gunnar et al., 2009). Adolescent and adult men typically show greater HPA reactivity to many types of stressors, including social stressors, than do adolescent and adult women (Bouma et al., 2009; Lopez-Duran et al., 2015; Stephens et al., 2016). The greater susceptibility of adolescent girls than boys to stressors, however, may not involve sex differences in HPA function per se, but rather sex differences in terms of the types of stressors to which they are exposed and/or sex differences in whether, and the extent to which, an event is considered a stressor (Oldehinkel and Bouma, 2011). A recent study highlights how pubertal phase is critical to understanding the relationship between

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HPA (dys)function and psychopathology; whereas the onset of a mood disorder was predicted by a hyporeactive HPA response to a laboratory stressor in girls in the earliest stages of puberty, a hyperreactive HPA response was predictive in later stages of pubertal development (Colich et al., 2015). Yet some studies that find pubertal status to be a relevant factor in stress reactivity in adolescence do not find sex to be a relevant factor (e.g., Hankin et al., 2015; Zhang et al., 2016). More direct studies of adolescents compared with adults are required to investigate whether there is an age-related change in the magnitude of the sex difference, or in the reversal of the direction of the sex difference, in people.

In rats, there have been few comparisons of adolescents and adults in glucocorticoid release in response to stressors, and the majority of these have involved prepubertal male adolescents. Prepubertal male rats tend to have higher and/or more prolonged release of corticosterone than do adults in response to 30 min of restraint stress (Bingham et al., 2011; Lui et al., 2012; Romeo et al., 2004a), intermittent footshock (Goldman et al., 1973), and ether inhalation (Vazquez and Akil, 1993). Prepubertal adolescents had lower corticosterone release than did adults after injection of nicotine (Cao et al., 2010; Cruz et al., 2008), paroxetine (Karanges et al., 2016), or lipopolysaccharide (Goble et al., 2011), and the two groups did not differ after administration of ethanol (Willey et al., 2012) or tetrahydrocannabinol (Schramm-Sapyta et al., 2007). The extent and direction of age differences depends in part on the type of stressor, which suggests that the critical differences between adolescents and adults may be in neural regions upstream from the paraventricular nucleus rather than in HPA function specifically.

We have conducted several studies involving acute responses to stressors in postpubertal male rats. Neither prepubertal (PND 30) nor postpubertal male rats (PND 45) differed in corticosterone concentrations from those of adults (either PND 70 or 85) after 1 h of isolation in small, ventilated containers and at time points during recovery (Hodges et al., 2014; Hodges and McCormick, 2015). The adolescents, however, showed more prolonged activation in the paraventricular nucleus of the hypothalamus (as indicated by expression of immediate early genes) after the isolation than did adults (Hodges et al., 2014; Hodges and McCormick, 2015), which is consistent with evidence of more prolonged stress responding in adolescents than in adults. In postpubertal male adolescents (PND 45), we found lower corticosterone concentrations compared with adults after 15 min of confinement to an elevated platform, but faster recovery to baseline concentrations in the adults than in the adolescents (McCormick et al., 2008). We found greater corticosterone release in response to 15 min of forced swim (Mathews et al., 2008b; Waters and McCormick, 2011) and in response to 30 min of restraint in postpubertal male adolescents (PND 45-47) than in adults. Thus, stress responses differ from adults for both prepubertal and postpubertal males, although there are differences between the two adolescent groups (Green and McCormick, 2016).

In adolescent females, there are reports of greater corticosterone release in response to 30 min of restraint in prepubertal than in adult females (Romeo et al., 2004b; Viau et al., 2005), and a report of reduced corticosterone release at 15 and 30 min into a 90 min restraint session compared with adult females (Doremus-Fitzwater et al., 2009). Postpubertal females did not differ from adults in corticosterone release in response to 15 min of confinement to an open arm (McCormick et al., 2008) or forced swim (Mathews et al., 2008b). PND 45, however, is a longer time post-puberty for female rats than it is for male rats; female adolescents may have greater corticosterone release to stressors at an earlier time after puberty than do adults. In contrast to the direction of the sex difference in humans, female rats have greater corticosterone release than do males in response to a wide-range of stressors (Goel et al., 2014). The sex differences in the HPA response to stress tend to increase after puberty in rats in keeping with the dampening effect of testosterone and the enhancing effect of estradiol on HPA function in rats (Handa and Weiser, 2014). Although results from a recent study indicate that testosterone may have the dampening effect on HPA responding in men that also is found in male rats (Stephens et al., 2016), the results from studies of sex hormones and HPA function in humans are largely inconsistent (Kajantie and Phillips, 2006). Nevertheless, there is evidence that the expression of human corticosteroid receptor genes is influenced by sex hormones, as has been found for rats (DeRijk and de Kloet, 2008).

In sum, the evidence of differences in HPA function across periods of ontogeny support that the risk associated with exposure to glucocorticoids will be specific to developmental stage. Further, the extensive, documented differences between adolescents and adults in neural structures that are substrates for glucocorticoid actions (Ahmed et al., 2015; Juraska and Willing, 2016; Shulman et al., 2016) indicate that even when faced with the same degree of glucocorticoid exposure, the consequences of the exposures will inevitably differ. Humans and rats, however, differ in the distribution of corticosteroid receptors across brain regions; there is relatively greater expression of glucocorticoid receptor expression in the neocortex in primates than in rodents (Pryce, 2008), and regions with highest receptor densities may be more susceptible to stressors. Glucocorticoid receptor polymorphisms are proving to be important factors in individual differences in HPA responses to stressors and the consequences thereof in humans, but comparable studies in rats are lacking. There is evidence, however, for stress-induced epigenetic modifications of the glucocorticoid receptor gene in both humans and rats (Li-Tempel et al., 2016; Radtke et al., 2015; Zhang et al., 2013).

In sum, puberty marks a change in HPA function in both humans and rats, which supports the use of rats as models in translational research on stress in adolescence.

4. Choice of stress procedure for a rat model of adolescent stress

Our review of chronic stress procedures in adolescent rats is not exhaustive, although we have tried to capture the main procedures used within the last 15 years. In addition, for studies involving rats of prepubertal ages, we have only included those that refer to that age as adolescence; our use of the search term adolescence may have omitted papers referring to the same age as juvenile. Table 1 describes the differences across labs in the procedures used and the ages, sex, and strain of rats involved.

4.1. Administration of exogenous corticosterone

Administering glucocorticoids either in drinking water, by subcutaneous injection, or through surgical implant of pellets rather than relying on stressor-induced elevations is an approach that has had much success, particularly as a preclinical model of depression (Sterner and Kalynchuk, 2010). Some of the advantages of exogenous administration of glucocorticoids is that it allows for better control of dosage, for example, by reducing the variability across individuals that stressors produce because of individual differences in the perception of stressors and by the reduction in corticosterone release that can occur to repeated exposures to a stressor (Sterner and Kalynchuk, 2010). There are a number of disadvantages. Direct comparisons of exogenous administration of corticosterone and of chronic stress show that the effects are sometimes different quantitatively (Conrad et al., 2007; Lussier et al., 2009), qualitatively (Conrad et al., 2004), or directionally

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Table 1
Procedures used as repeated or chronic stressors in studies of adolescent rats.

Repeated/Chronic stress procedure			
Sex[a] & strain[b]	Ages[c] (Days)	Description of procedure	References
Exogenous Corticosterone			
♀/♂ SD	30–50	Drinking water (50 μg/mL for 14 days, then 25 and 12.5 μg/mL for 3 days each)	(Bertholomey et al., 2016)
♂ SD	30–50	Drinking water (50 μg/mL for 14 days, then 25 and 12.5 μg/mL for 3 days each)	(Torregrossa et al., 2012)
♀/♂ Wistar outbred	**56–76**	Drinking water (50 μg/mL)	(Hill et al., 2014)
♂ SD	27–33	Drinking water (200 μg/mL)	(Den et al., 2014)
♀/♂ SD	30–58	Drinking water (150 or 300 μg/mL)	(Kaplowitz et al., 2016)
♂ LE	30–45	Drinking water (400 μg/mL)	(Waters and McCormick, 2011)
♂ Lister	24–30	S.C. pellet (62.5 mg)	(Bush et al., 2003)
♂ Wistar outbred	**~56–70**	S.C. pellet (100 mg)	(Choy and van den Buuse, 2008)
♂ SD	28–42	S.C. pellet (50 or 200 mg)	(Lee et al., 2003)
♂ Wistar Han	28–42	Injection (7x, 1 per day, 5 mg/kg)	(Veenit et al., 2013)
♂ LE	30–45	Injection (16x, daily, 40 mg/kg)	(Waters and McCormick, 2011)
Restraint			
♂ SD	28–55	5 min (28 sessions)	(Suo et al., 2013)
♂ Wistar	~100 g age ??	10 min (6 sessions, 2 per day)	(Kusek et al., 2013)
♂ SD	29–37	20 min (7 sessions)	(Zhang and Rosenkranz, 2016)
♂ SD	32–40	20 min (7 sessions)	(Padival et al., 2015)
♀ Fischer	**55–62**	20 min (8 sessions)	(Panagiotakopoulos et al., 2015)
♂ Wistar Han	28–42	20 min (15 sessions)	(Hetzel and Rosenkranz, 2014)
♂ SD	35–44	30 min (10 sessions)	(Lee and Hill, 2013)
♀/♂ Wistar	26–32	1 h (7 sessions)	(Traslaviña et al., 2014)
♀/♂ Wistar	31–37	1 h (7 sessions)	(Dayi et al., 2015)
♂ Wistar	28–37	1 h (10 sessions)	(Duarte et al., 2015a; Duarte et al., 2015b)
♀/♂ SD	30–52	1 h (12 sessions)	(Barha et al., 2011)
♂ SD	29–33	1.5 h (5 sessions)	(Anderson et al., 2013)
♀/♂ SD	38–42	1.5 h (5 sessions)	(Varlinskaya et al., 2013)
♂ SD or Wistar	30–34	2 h (5 sessions)	(Fernández et al., 2016)
♀ SD	25–31	2 h (7 sessions)	(Lee and Noh, 2015)
♂ SD	28–34 or 42–48	2 h (7 sessions)	(Bingham et al., 2011)
♂ SD	42–48	3 h (7 sessions)	(Negrón-Oyarzo et al., 2014)
♂ SD	42–49	3 h (7 sessions)	(Negrón-Oyarzo et al., 2015)
♂ SD	26–46	6 h (21 sessions)	(Gillette et al., 2015)
Predation Stress			
♀/♂ LE	40–48	Cat odour (5 sessions)	(Wright et al., 2008)
♀/♂ LE	~38–46	Cat odour (5 sessions)	(Wright et al., 2012; Wright et al., 2013)
♂ Wistar albino	28–60	Cat fur (17 sessions)	(Kendig et al., 2011)
Social Stressors			
Social Isolation		Housed singly continuously	
♂ Wistar	21–36		(Cuenya et al., 2015)
♀ SD	21–42		(Lukkes et al., 2012)
♂ SD	21–42		(Lukkes et al., 2009a; Lukkes et al., 2009b; Lukkes et al., 2009c)
♂ Wistar	21–48		(Sonei et al., 2016)
♂ SD	~21–51		(Biggio et al., 2014)
♂ SD	22–28		(Granholm et al., 2015)
♂ SD	28–46		(Caruso et al., 2014)
♂ Wistar	28–48		(Cruz et al., 2016)
♂ Fischer	28–53		(Hori et al., 2014)
♂ LE	28–70		(Karkhanis et al., 2015)
♂ LE	28–70		(Skelly et al., 2015)
♂ LE	28–85		(Rau et al., 2015)
♀/♂ SD	30–50		(Hong et al., 2012; Weintraub et al., 2010)
♀ LE	30–70		(Butler et al., 2014)
Social Defeat or Resident-Intruder			
♂ Wistar or WTG	45–46	Defeated by resident (2x)	(Vidal et al., 2011b)
♂ WTG	45–46	Defeated by resident then placed behind wire mesh in resident's cage (2x)	(Coppens et al., 2011)
♂ LE	35–44	Defeated by resident (4x)	(Burke and Miczek, 2015)
♂ Wistar or WTG	45–58	Defeated by resident (5x)	(Vidal et al., 2011a)
♂ Wistar	45–57	Defeated by resident (2x), placed behind wire mesh in resident's cage (3x)	(Vidal et al., 2007)
♂ WTG	45–57	Defeated by resident (2x), placed behind wire mesh in resident's cage (3x)	(Coppens et al., 2014)
♂ Roman	45–57	Defeated by resident (2x), placed behind wire mesh in resident's cage (3x)	(Vidal et al., 2007)
♂ SD	42–55	Defeated by resident then placed behind wire mesh in resident's cage (5x)	(Zitnik et al., 2015)
♂ SD	35–39	Defeated by resident then placed behind wire mesh in resident's cage (5x)	(Burke et al., 2010; Burke et al., 2011; Novick et al., 2016; Watt et al., 2009; Watt et al., 2014)

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Table 1 (*continued*)

Repeated/Chronic stress procedure			
Sex[a] & strain[b]	Ages[c] (Days)	Description of procedure	References
♀ SD	28–32 or 42–46	Defeated by resident then placed behind wire mesh in resident's cage (5x)	(Snyder et al., 2015a)
♂ SD	28–32 or 42–46	Defeated by resident then placed behind wire mesh in resident's cage (5x)	(Snyder et al., 2015b)
♂ SD	28–34 or 42–48	Defeated by resident (7x)	(Bingham et al., 2011)
♀ SD	~36–~45	Defeated by resident then placed behind wire mesh in resident's cage (7x)	(Ver Hoeve et al., 2013)
♂ and ♀ LE	45–54	Defeated by resident then placed behind wire mesh in resident's cage (10x)	(Furuta et al., 2015)
♂ Wistar (1) or SD (2)	28–34 (1) or 35–41 (2)	(1) Defeated by resident (2x), placed behind wire mesh in resident's cage (1x) (2): Defeated by resident (10x)	(Buwalda et al., 2013)
♂ Wistar	28–50	Defeated by resident then placed behind wire mesh in resident's cage (23x)	(Bourke et al., 2014)
Social Instability			
♀ Wistar	30–38	1 h isolation then paired with new cage partner (9 sessions)	(Raftogianni et al., 2012)
♂ LE	30–45	1 h isolation then paired with new cage partner (16 sessions)	(Cumming et al., 2014; Green et al., 2013; Green and McCormick, 2013a; Hodges and McCormick, 2015; McCormick et al., 2013a; McCormick et al., 2012; Morrissey et al., 2011)
♀ LE	30–45	1 h isolation then paired with new cage partner (16x)	(McCormick et al., 2013b; McCormick et al., 2010)
♀/♂ LE	30–45	1 h isolation then paired with new cage partner (16 sessions)	(Mathews et al., 2008a; Mathews et al., 2008b; McCormick et al., 2008)
♀/♂ LE	33–48	1 h isolation then paired with new cage partner (16 sessions)	(McCormick et al., 2004; McCormick et al., 2005)
♂ SD	28–62	1 h isolation then paired with new cage partners (35 sessions)	(Tsai et al., 2014)
Chronic Unpredictable Stress/Chronic Variable Stress			
♀ SD	31–41	2 per day: soiled bedding, cage tilt, elevated platform, restraint, novel bedding, overnight isolation, water deprivation.	(Comeau et al., 2015)
♂ SD	30–70	6 per week: 2 physical (small cage, wet bedding, cage tilt); 2 social (isolation, crowding, foreign bedding); 2 predation (taxidermied bobcat nearby, cat fur, feline vocalizations).	(Chaby et al., 2015b; Chaby et al., 2015c)
♂ SD	30–78	6 per week: 2 physical (small cage, wet bedding, cage tilt); 2 social (isolation, crowding, foreign bedding); 2 predation (taxidermied bobcat, cat and fox urine, feline vocalizations).	(Chaby et al., 2015a)
♂ LE	30–70	6 per week: 3 physical (small cage, wet bedding, cage tilt), 3 social (isolation, crowding, foreign bedding)	(Chaby et al., 2013)
♀ SD	42–48	Each stressor once: forced swim (warm and cold water), isolation, food deprivation, water deprivation, overnight light, elevated platform (3x), foot shock (10x), crowding with constant light.	(Zaidan and Gaisler-Salomon, 2015)
♂ bLR SD	35–60	>9 per week with increasing frequency: exposure to damp bedding, white noise, lighting, food deprivation, water deprivation, cage tilt, stroboscopic light, predator odour.	(Rana et al., 2016)
♀/♂ Wistar Han	28–42	1-2 stressors on 7 of the days: novel box, TMT odour, bright light, elevated platform.	(Toledo-Rodriguez and Sandi, 2011)
♀/♂ Wistar Han	28–30	Daily exposure: TMT odour, elevated platform	(Toledo-Rodriguez and Sandi, 2007)
♂ SD	28–55	1 stressor per day; for social stress: isolation, novel environment, crowding, litter-shifting, subordination (resident-intruder); for physical stress: cold, ether, forced swim, restraint, loud noise	(Kabbaj et al., 2002)
♀/♂ Fischer	37–44	2-3 per day: restraint, exposure to cold (4° C), food deprivation, wet bedding, swim stress, crowding.	(Taylor et al., 2013)
♂ SD	33–35	One per day: forced swim, elevated platform (3x), foot shock (6x)	(Tsoory and Richter-Levin, 2006)
♂ SD	27–29	One per day: forced swim, elevated platform (3x), foot shock (6x)	(Saul et al., 2012)
♂ LE	26–35	2 per day: forced swim, tail pinch, cat fur, restraint.	(Wright et al., 2015)
♂ Wistar	28–37	2 per day: forced swim, restraint, lights on overnight, lights off during the day, humid sawdust, cold stress, food and water deprivation, isolation.	(Duarte et al., 2015b)

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Table 1 (*continued*)

Repeated/Chronic stress procedure			
Sex[a] & strain[b]	Ages[c] (Days)	Description of procedure	References
♂ SD	~38–42	2 per day: soiled bedding, cage tilt, elevated platform, restraint, novel cage, overnight isolation, tail pinching.	(Comeau et al., 2014)
♂ Wistar Han	28–42	On 7 of 15 days: open field, TMT, elevated platform.	(Veenit et al., 2014)
♂ Wistar	28–37	2 per day: restraint, wet bedding, cold exposure, lights off, lights on, food and water deprivation, isolation, forced swim.	(Cruz et al., 2012)
♂ SD	27–33	1 per day, every other day: restraint, elevated platform (2x), footshock (40x)	(Luo et al., 2014)
♂ SD	35–50	2 per day: restraint, rotation, forced swim, cage tilt, wet sawdust, crowding, cold, reverse light-cycle, food and water deprivation, tail pinch.	(Xu et al., 2016)
♀ SD	45–58	2 per day: agitation, cold, open field, hypoxia, restraint.	(Wulsin et al., 2016)
♂ LE	45–51	One per day: restraint, TMT, tail pinch	(Handy et al., 2016)
♂ SD	28–48	2 per day: cold, water deprivation, agitation, tilted cage, forced swim (cold), crowding, soiled bedding, light-cycle reversal, food deprivation, tail pinch.	(Suo et al., 2013)
♀/♂ LE	22–33 or 35- 46	6 out of 12 days: water immersion, elevated platform, or foot shock.	(Wilkin et al., 2012)
♂ SD	~42–~62	One per day: forced swim, cage rotation, isolation, damp bedding, food and water deprivation, restraint, strobe light, cage tilt.	(Reich et al., 2013)
♀/♂ Wistar	37–48	One per day: social defeat, restraint	(Bourke et al., 2013)
♀/♂ Wistar	37–49	One per day: social defeat, restraint	(Bourke and Neigh, 2011; Harrell et al., 2015; Kelly et al., 2014; Pyter et al., 2013)
♀/♂ SD	37–49	One per day: social defeat, restraint	(Harrell et al., 2013)

Notes.
[a] Grey shading is used when the experiments were in female rats or included female rats.
[b] LE = Long Evans; SD = Sprague Dawley; WTG = wild-type Groeningen; bred Low Responders Sprague Dawley.
[c] Grey shading is used to indicate when stress procedures were applied at peripubertal ages (includes ages > 35 for females and >42 for males). Bold font indicates that stress procedures were applied post-pubertally only (>35 for females and >42 for males).

(Nacher et al., 2004). Because of individual differences in intake, administration in the drinking water does not permit the control over dosage that injection does; age differences in intake also make the comparison of adolescent versus adult treatment difficult because of the resulting dosage differences (Waters and McCormick, 2011). A problem with the other modes of administration, however, is the greater susceptibility of adolescents than adults to stress of injection and of surgery (e.g., Keeley et al., 2015; O'Shea et al., 2004; Raap et al., 2000).

4.2. Predator stress

Predator stress is a naturalistic stressor that can be readily adapted for use in the laboratory. Olfaction is a critical sensory system for guiding behaviour in rats, and thus olfactory stimuli can be used without introducing prey animals to the lab. Scents as diverse as 2-propylthietane (in weasel anal secretions), 2,5-dihydro-2,4,5-trimethylthiazoline (in fox anal secretions), cat fur or ferret fur odour, fox urine, all result in increased HPA responding (Hegab and Wei, 2014), although the specific neural regions activated differed across odours (Takahashi, 2015). In addition, some strains of rats are more sensitive to some odours than are other strains (Staples, 2010). A direct comparison of adolescent and adults rats found greater neuroendocrine responses to cat odour in the younger group than in the older group (Wright et al., 2012), which is of translational relevance for exploring the greater susceptibility of adolescents than adults to stressors.

4.3. Restraint stress

Restraint stress involves confining the animal in a space, typically a hemi-cylindrical ventilated plastic tube or similar device made of mesh. Restraint stress differs from immobilization stress; whereas immobilization stress involves preventing movement with devices attached to head and paws, restraint stress restricts movement because of the dimensions of the space but does not prevent movement. An advantage of the use of restraint stress is that it is one of the most commonly used means of investigating stress responses and their consequences, and thus there is a vast literature in adult rats available for reference. The effects of restraint stress are considered to be the result of distress of being confined rather than any lasting effect of any physical discomfort (Buynitsky and Mostofsky, 2009). In studies with adult rats, restraint stress has been applied in repeated sessions of 5 min to several hours, and up to 6 h per day for 21 days (e.g., Conrad et al., 2003). The studies that have investigated the lasting effects of the most severe exposures have found many of the effects to dissipate with time when the chronic stress was experienced in adulthood (e.g., Radley et al., 2005). When restraint was experienced for shorter durations in adolescence, effects on HPA function and neurogenesis were evident several weeks after the last exposure (Barha et al., 2011), which is consistent with the hypothesis that adolescents are more vulnerable than are adults to stressors.

4.4. Social stressors

4.4.1. Social defeat/Resident-intruder stress

There are many different models of social defeat stress, though the commonality across procedures involves subjugating the experimental animal (intruder) to attack from an aggressive male (resident) that is defending its territory (reviewed in Hammels et al., 2015). After a number of physical attack sessions, the

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psychological stress can be maintained by keeping the intruder near the resident but separated by a barrier. This model has proven to be an excellent model for understanding stress-induced dysfunction in adult rats, but it is a model that involves a number of challenges. Finding an aggressive male to act as the aggressor can be challenging, and retired breeders are more likely to be effective residents than are randomly selected male rats. Females are not as territorial as are males, and high probabilities of attacking are found usually only when the female is lactating (Toth and Neumann, 2013); thus the procedure is more difficult to apply in females. Further, there is significant variation between residents and within residents from bout to bout, which may increase the variability in the results obtained (reviewed in MacKay, 2016). Further, residents are much less aggressive toward an adolescent than toward an adult intruder, and there are many qualitative differences between the interactions of resident-adolescent intruder pairs and interactions of resident-adult intruder pairs (Burke and Miczek, 2015). Both adolescent and adult rats that experience social defeat, however, display a number of long-lasting changes in behavioural and neural function, particularly if housed singly after the exposures (Buwalda et al., 2011).

4.4.2. Social isolation

Social isolation deprives the animal of all social contact by having it housed alone for extended periods (usually more than three weeks or more) and has been referred to as a form of "sociogenic brain damage" or social malnourishment (Montagu, 1977). Although adult rats show a number of deficits after long periods of social deprivation from social isolation housing, adolescents are more susceptible (Einon and Morgan, 1977; Panksepp and Beatty, 1980), and some remediation may be possible from a return to social housing (Hellemans et al., 2004; Hol et al., 1999). Social isolation housing has been referred to as a stressor; nevertheless, the procedure does not involve a steep rise and prolonged elevation in glucocorticoids that is characteristic of other stress exposures, and instead may involve dysfunction resulting from minimal stimulation (reviewed in Green and McCormick, 2013a). Thus, although this model highlights the importance of social contact particularly in the adolescent period and has been used as a model of more severe psychopathology (e.g., schizophrenia, Fone and Porkness, 2008), it may be less useful as a translational model for adolescent stress. In humans, variation in the quality of social relationships rather than the absence versus presence of social contact is likely of greater relevance for understanding risk and resilience for the majority of psychiatric conditions.

4.4.3. Social instability

Social instability stress involves changing the social housing conditions of rats. Although this procedure usually involves changing the membership of individuals that are housed together, sometimes it also has involved periods of isolation housing and periods of overcrowding (Herzog et al., 2009). The rotation of membership in mixed-sex colonies increases aggression and results in elevations in circulating corticosterone (Haller et al., 1999). When the social instability involves changes in pair-housed rats of the same sex, little aggression is observed in either adult or adolescent males and females and the elevation in corticosterone that arises from a change in cage partner is short-lived (Hodges and McCormick, 2015; McCormick et al., 2007). We have used change of cage partners after 1 h of isolation in small containers (akin to restraint stress) as our model of social instability stress. Whereas adults readily habituate to the repeated change of cage partner after the 1 h isolation, adolescents instead show potentiated corticosterone release to repeated change in cage partners despite some habituation to repeated 1 h isolation stress (Hodges and McCormick, 2015). We have found long-lasting effects of our social instability procedure on cognitive and emotional behaviours and behavioural responses to drugs of abuse, effects that are not observed when the procedure is applied to adults (reviewed in McCormick, 2010; McCormick et al., 2015), which suggests that the procedure may capture adolescent-specific plasticity. Many of the differences in social behaviour evident in rats as adults after adolescent social instability stress (reviewed in McCormick et al., 2015) parallel those observed after depriving adolescents of social play, suggesting that the quality of social interactions in adolescence may be as important as their presence versus absence (Hol et al., 1999; van den Berg et al., 1999).

4.5. Chronic unpredictable stress/chronic variable stress

The use of a lengthy schedule involving the application of diverse physical and psychological stressors (e.g., electric shock, period of isolation, immobilization, cage tilt, wet bedding, water deprivation, etc.) one to several stressors experienced daily for 21 days and up to 3 months has been used as an effective model of depression in adult rats (reviewed in Qiao et al., 2016). The use of different stressors prevents the reduction in corticosterone release that can occur when the same stressor is administered repeatedly. Nevertheless, the impairments typically dissipate with time when applied to adult male rats whether the procedure involves repeated exposure to the same stressor (repeated restraint) or involves varied, and more severe stressors than restrain (Bian et al., 2012; Heine et al., 2004). In contrast, a lengthy period of exposures to chronic mild stressors from PND days 30 through 78 resulted in increased anxiety that continued to be evident six months after the exposures (Chaby et al., 2015a). Typically, a much shorter schedule of stressor exposures are used in adolescent rats than in adult rats. Nevertheless, direct comparisons of chronic variable stress exposures administered in adolescence versus administered in adulthood are lacking; such studies would help pinpoint the extent to which adolescents are uniquely vulnerable.

5. Conclusions

Although the wide variety in stress procedures, ages at which they are applied, and strain of rat makes comparison of findings across studies difficult, the evidence is consistent with the hypothesis that adolescence is a period of life in which the response to stressors and the consequences of stressors differ from those in other times of life. The definition of adolescence for rats, however, is not always consistent with that used for humans. As indicated in Table 1, the majority of stress procedures have been applied peripubertally, and usually the stressors are applied mostly in the prepubertal period, and, in several studies, only on prepubertal days of age. There are far fewer studies of female rats, and when females have been included, they typically were tested at the same age as males. Because of their earlier onset of puberty, the studies of females were more likely to include a lengthier postpubertal period than those in males. As we described earlier, there are marked differences between the prepubertal and postpubertal rat beyond gonadal status.

There is increasing awareness in human research that both the timing of puberty and the phase of puberty are important factors in adolescent psychological development, and that these factors should receive greater attention by researchers (Berenbaum et al., 2015). For example, a recent study found that exposure to trauma during puberty (defined as the two years after the onset of menarche) led to greater risk of developing an anxiety disorder than exposures at earlier or later times (Marshall, 2016). Thus, greater attention to the timing of puberty in research with rats may

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increase the translational relevance of the research.

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